

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims**

1. (Currently amended) A method for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype, said method comprising the steps of:

- a) observing in a test subject having an inflammatory disease-associated genotype comprising at least one inflammatory disease-associated allele selected from the group consisting of allele 3 of the 222/223 marker of IL-1A, allele 4 of the 222/223 marker of IL-1A, allele 3 of the gz5/gz6 marker of IL-1A, allele 4 of the gz5/gz6 marker of IL-1A, allele 1 of the -889 marker of IL-1A, allele 2 of the -889 marker of IL-1A, allele 1 of the +3954 marker of IL-1B, allele 2 of the +3954 marker of IL-1B, allele 1 of the -511 marker of IL-1B, allele 2 of the -511 marker of IL-1B, allele 3 of the gaat.p333330 marker, allele 4 of the gaat.p333330 marker, allele 3 of the Y31 marker, allele 6 of the Y31 marker, allele 1 of the +2018 marker of IL-1RN, allele 2 of the +2018 marker of IL-1RN, allele 1 of the +4845 allele of IL-1A, allele 2 of the +4845 allele of IL-1A, allele 1 of the VNTR marker of IL-1RN, allele 2 of the VNTR marker of IL-1RN, and allele 2 of the +6912 marker of IL-1B ~~an IL-1A allele, an IL-1B allele, an IL-1RN allele, a TNF-A allele and an IL-13 allele,~~ a biomarker;
- b) contacting said test subject with a test substance;
- c) observing again in said test subject said biomarker; and,
- d) administering an inducer to the test subject prior to or concomitant with observing said biomarker,

wherein a change in said biomarker from an inflammatory disease-associated phenotype to a non-inflammatory disease-associated phenotype identifies a test substance that is likely to prevent or diminish the specific biological response in a subject having said inflammatory disease-associated genotype.

2. (Cancelled)

3. (Currently amended) A method of claim 1, wherein said subject has at least two ~~one~~ inflammatory disease-associated alleles from the IL-1 44112332 haplotype or the IL-1 33221461 haplotype.

4. (Previously presented) A method of claim 1, wherein said subject has at least one allele selected from the group consisting of allele 1 of IL-1A (+4845), allele 4 of IL-1A (222/223), allele 4 of IL-1A (gz5/gz6), allele 1 of IL-1A (-889), allele 2 of IL-1B (-511), allele 2 of gaat.p33330, allele 3 of Y31, allele 2 of IL-1RN (+2018), allele 2 of IL-1RN (1731), allele 2 of IL-1RN (1812), allele 2 of IL-1RN (1868), allele 2 of IL-1RN (1887), allele 2 of IL-1RN (8006), allele 2 of IL-1RN (8061), allele 2 of IL-1RN (9589), allele 2 of IL-1A (+4845), allele 3 of IL-1A (222/223), allele 3 of IL-1A (gz5/gz6), allele 2 of IL-1A (-889), allele 1 of IL-1B (-511), allele 4 of gaat.p33330, allele 6 of Y31, allele 1 of IL-1RN (+2018), allele 2 of IL-1B (+6912), allele 2 of TNFA (-308), allele 2 of TNFA (-238), and allele 2 of IL-13 (+2581).

5. (Previously presented) A method of claim 1, wherein said inflammatory disease-associated genotype is associated with a predisposition to a disease selected from the group consisting of periodontal disease, coronary artery disease, atherosclerosis, Alzheimer's disease, osteoporosis, insulin-dependent diabetes, diabetic retinopathy, end-stage renal disease, diabetic nephropathy, hepatic fibrosis, alopecia areata, Graves' disease, Graves' ophthalmopathy, extrathyroid disease, systemic lupus erythematosus, lichen sclerosis, rheumatoid arthritis, juvenile chronic arthritis, gastric cancer, ulcerative colitis, asthma, multiple sclerosis, interstitial lung disease, idiopathic pulmonary fibrosis, sepsis and acne.

6. (Previously presented) A method of claim 1, wherein said subject is homozygous for an allele selected from the group consisting of: allele 1 of IL-1A (+4845), allele 4 of IL-1A (222/223), allele 4 of IL-1A (gz5/gz6), allele 1 of IL-1A (-889), allele 2 of IL-1B (-511), allele 3

of gaat.p33330, allele 3 of Y31, allele 2 of IL-1RN (+2018), allele 2 of IL-1RN (1731), allele 2 of IL-1RN (1812), allele 2 of IL-1RN (1868), allele 2 of IL-1RN (1887), allele 2 of IL-1RN (8006), allele 2 of IL-1RN (8061), allele 2 of IL-1RN (9589), allele 2 of IL-1A (+4845), allele 3 of IL-1A (222/223), allele 3 of IL-1A (gz5/gz6), allele 2 of IL-1A (-889), allele 1 of IL-1B (-511), allele 4 of gaat.p33330, allele 6 of Y31, allele 1 of IL-1RN (+2018), allele 2 of IL-1B (+6912), allele 2 of TNFA (-308), allele 2 of TNFA (-238), and allele 2 of IL-13 (+2581).

7. (Previously presented) A method of claim 1, wherein said biomarker is selected from the group consisting of: electrocardiogram parameters, pulmonary function, core body temperature, blood or urine IL-1 $\alpha$  levels, blood or urine IL-1 $\beta$  levels, blood levels of soluble IL-1 receptors, blood or urine IL-13 levels, blood or urine IL-6 levels, blood or urine TNF $\alpha$  levels, blood levels of stable eicosanoids, nitric oxide levels, white blood cell count, blood lipid levels, red blood cell count, platelet count, blood iron levels, blood zinc levels, blood neopterin level, blood reactive oxygen species, blood levels of C reactive protein, blood levels of fibrinogen, steroid hormone levels, standard urine parameters, size of skin erythema, and duration of skin erythema.

8. (Cancelled)

9. (Previously presented) A method of claim 1, wherein said inducer comprises exercise sufficient to cause exercise induced stress.

10. (Previously presented) A method of claim 9, wherein said exercise is a treadmill stress test.

11. (Previously presented) A method of claim 1, wherein said inducer comprises a subcutaneous injection of an irritant.

12. (Previously presented) A method of claim 11, wherein said irritant induces a monocytic inflammatory response.
13. (Previously presented) A method of claim 11, wherein the irritant is urate crystals.
14. (Previously presented) A method of claim 11 wherein the irritant is monosodium urate crystals.
15. (Previously presented) A method of claim 11, wherein said at least one biomarker includes the dimensions or duration of skin erythema resulting from said subcutaneous injection.
16. (Currently amended) A method for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype, said method comprising the steps of:
- a) providing a cell from a test subject, having an inflammatory disease-associated genotype comprising at least one inflammatory disease-associated allele selected from the group consisting of an allele 3 of the 222/223 marker of IL-1A, allele 4 of the 222/223 marker of IL-1A, allele 3 of the gz5/gz6 marker of IL-1A, allele 4 of the gz5/gz6 marker of IL-1A, allele 1 of the -889 marker of IL-1A, allele 2 of the -889 marker of IL-1A, allele 1 of the +3954 marker of IL-1B, allele 2 of the +3954 marker of IL-1B, allele 1 of the -511 marker of IL-1B, allele 2 of the -511 marker of IL-1B, allele 3 of the gaat.p333330 marker, allele 4 of the gaat.p333330 marker, allele 3 of the Y31 marker, allele 6 of the Y31 marker, allele 1 of the +2018 marker of IL-1RN, allele 2 of the +2018 marker of IL-1RN, allele 1 of the +4845 allele of IL-1A, allele 2 of the +4845 allele of IL-1A, allele 1 of the VNTR

marker of IL-1RN, allele 2 of the VNTR marker of IL-1RN, and allele 2 of the +6912 marker of IL-1B ~~IL-1A allele, an IL-1B allele, an IL-1RN allele, a TNF-A allele and an IL-13 allele;~~

- b) observing in said cell, or a cell propagated therefrom, a biomarker;
- c) contacting said cell with a test substance;
- d) observing again in said cell said biomarker; and
- e) contacting said cells with an inducer prior to or concomitant observing said biomarker,

wherein a change in said biomarker from an inflammatory disease-associated phenotype to a non-inflammatory disease-associated phenotype identifies a test substance that is likely to prevent or diminish the specific biological response in a subject.

17. (Cancelled).

18. (Previously presented) A method of claim 16, wherein said subject has at least two ~~one~~ inflammatory disease-associated alleles from the IL-1 44112332 haplotype or the IL-1 33221461 haplotype.

19. (Previously presented) A method of claim 16, wherein said subject has at least one allele selected from the group consisting of allele 1 of IL-1A (+4845), allele 4 of IL-1A (222/223), allele 4 of IL-1A (gz5/gz6), allele 1 of IL-1A (-889), allele 2 of IL-1B (-511), allele 3 of gaat.p33330, allele 3 of Y31, allele 2 of IL-1RN (+2018), allele 2 of IL-1RN (1731), allele 2 of IL-1RN (1812), allele 2 of IL-1RN (1868), allele 2 of IL-1RN (1887), allele 2 of IL-1RN (8006), allele 2 of IL-1RN (8061), allele 2 of IL-1RN (9589), allele 2 of IL-1A (+4845), allele 3 of IL-1A (222/223), allele 3 of IL-1A (gz5/gz6), allele 2 of IL-1A (-889), allele 1 of IL-1B (-

511), allele 4 of gaat.p33330, allele 6 of Y31, allele 1 of IL-1RN (+2018), allele 2 of IL-1B (+6912), allele 2 of TNFA (-308), allele 2 of TNFA (-238), and allele 2 of IL-13 (+2581).

20. (Previously presented) A method of claim 16, wherein said inflammatory disease-associated genotype is associated with a predisposition to a disease selected from the group consisting of periodontal disease, coronary artery disease, atherosclerosis, Alzheimer's disease, osteoporosis, insulin-dependent diabetes, diabetic retinopathy, end-stage renal disease, diabetic nephropathy, hepatic fibrosis, alopecia areata, Graves' disease, Graves' ophthalmopathy, extrathyroid disease, systemic lupus erythematosus, lichen sclerosis, rheumatoid arthritis, juvenile chronic arthritis, gastric cancer, ulcerative colitis, asthma, multiple sclerosis, interstitial lung disease, idiopathic pulmonary fibrosis, sepsis and acne.

21. (Previously presented) A method of claim 16, wherein said subject is homozygous for an allele selected from the group consisting of: allele 1 of IL-1A (+4845), allele 4 of IL-1A (222/223), allele 4 of IL-1A (gz5/gz6), allele 1 of IL-1A (-889), allele 2 of IL-1B (-511), allele 3 of gaat.p33330, allele 3 of Y31, allele 2 of IL-1RN (+2018), allele 2 of IL-1RN (1731), allele 2 of IL-1RN (1812), allele 2 of IL-1RN (1868), allele 2 of IL-1RN (1887), allele 2 of IL-1RN (8006), allele 2 of IL-1RN (8061), allele 2 of IL-1RN (9589), allele 2 of IL-1A (+4845), allele 3 of IL-1A (222/223), allele 3 of IL-1A (gz5/gz6), allele 2 of IL-1A (-889), allele 1 of IL-1B (-511), allele 4 of gaat.p33330, allele 6 of Y31, allele 1 of IL-1RN (+2018), allele 2 of IL-1B (+6912), allele 2 of TNFA (-308), allele 2 of TNFA (-238), and allele 2 of IL-13 (+2581).

22. (Previously presented) A method of claim 16, wherein said biomarker is selected from the group consisting of: IL-1 $\alpha$  production, IL-1 $\beta$  production, prostanoid production, TNF $\alpha$  production, large-scale gene transcript level analysis, and large-scale protein level analysis.

23. (Previously presented) A method of claim 16, wherein said cell is an immune cells.

24-25. (Cancelled)

26. (Previously presented) A method of claim 16, wherein said inducer is a substance known to activate IL-1 production in monocytes or macrophages.

27. (Previously presented) A method of claim 16, wherein said inducer is selected from the group consisting of a lipopolysaccharide, concanavalin A, phytohemagglutinin, phorbol myristic acid (PMA), a calcium ionophore, interferon gamma, interleukin-12, interleukin-1, TNF $\alpha$ , UV radiation, and ionizing radiation.

28. - 37. (Cancelled)

38. (Currently amended) A method for identifying a substance that is likely to increase a specific biological response in a subject having an inflammatory disease-associated genotype, said method comprising the steps of:

- a) observing in a test subject having an inflammatory disease-associated genotype comprising at least one inflammatory disease-associated allele selected from the group consisting of allele 3 of the 222/223 marker of IL-1A, allele 4 of the 222/223 marker of IL-1A, allele 3 of the gz5/gz6 marker of IL-1A, allele 4 of the gz5/gz6 marker of IL-1A, allele 1 of the -889 marker of IL-1A, allele 2 of the -889 marker of IL-1A, allele 1 of the +3954 marker of IL-1B, allele 2 of the +3954 marker of IL-1B, allele 1 of the -511 marker of IL-1B, allele 2 of the -511 marker of IL-1B, allele 3 of the gaat.p333330 marker, allele 4 of the gaat.p333330 marker, allele 3 of the Y31 marker, allele 6 of the Y31 marker, allele 1 of the +2018 marker of IL-1RN, allele 2 of the +2018 marker of IL-1RN, allele 1 of the

+4845 allele of IL-1A, allele 2 of the +4845 allele of IL-1A, allele 1 of the VNTR marker of IL-1RN, allele 2 of the VNTR marker of IL-1RN, and allele 2 of the +6912 marker of IL-1B ~~an IL-1A allele, an IL-1B allele, an IL-1RN allele, a TNF-A allele and an IL-13 allele,~~ a biomarker;

- b) contacting said test subject with a test substance;
- c) observing again in said test subject said biomarker; and,
- d) administering an inducer to the test subject prior to or concomitant with observing said biomarker,

wherein a change in said biomarker from an inflammatory disease-associated phenotype to a non-inflammatory disease-associated phenotype identifies a test substance that is likely to increase the specific biological response in a subject having said inflammatory disease-associated genotype.

39. (Currently amended) A method for identifying a substance that is likely to increase a specific biological response in a subject having an inflammatory disease-associated genotype, said method comprising the steps of:

- a) providing a cell from a test subject, having an inflammatory disease-associated genotype comprising at least one inflammatory disease-associated allele selected from the group consisting of allele 3 of the 222/223 marker of IL-1A, allele 4 of the 222/223 marker of IL-1A, allele 3 of the gz5/gz6 marker of IL-1A, allele 4 of the gz5/gz6 marker of IL-1A, allele 1 of the -889 marker of IL-1A, allele 2 of the -889 marker of IL-1A, allele 1 of the +3954 marker of IL-1B, allele 2 of the +3954 marker of IL-1B, allele 1 of the -511 marker of IL-1B, allele 2 of the -511 marker of IL-1B, allele 3 of the gaat.p333330 marker, allele 4 of the gaat.p333330 marker, allele 3 of the Y31 marker, allele 6 of the Y31 marker, allele 1 of the +2018 marker of IL-1RN, allele 2 of the +2018 marker of IL-1RN, allele 1 of the +4845 allele of IL-1A, allele 2 of the +4845 allele of IL-1A, allele 1 of the VNTR marker of IL-1RN, allele 2 of the VNTR marker of IL-1RN, and allele 2 of the



~~+6912 marker of IL-1B an IL-1A allele, an IL-1B allele, an IL-1RN allele, a  
TNF-A allele and an IL-13 allele;~~

- b) observing in said cell, or a cell propagated therefrom, a biomarker;
- c) contacting said cell with a test substance;
- d) observing again in said cell said biomarker; and
- e) contacting said cells with an inducer prior to or concomitant observing said biomarker,

wherein a change in said biomarker from an inflammatory disease-associated phenotype to a non-inflammatory disease-associated phenotype identifies a test substance that is likely to increase the specific biological response in a subject.

40. (new) A method for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype, said method comprising the steps of:

- a) observing in a test subject having an inflammatory disease-associated genotype comprising an IL-1B (-511) allele 2 and an IL-1B (-3954) allele 2, a biomarker;
- b) contacting said test subject with a test substance;
- c) observing again in said test subject said biomarker; and,
- d) administering an inducer to the test subject prior to or concomitant with observing said biomarker,

wherein a change in said biomarker from an inflammatory disease-associated phenotype to a non-inflammatory disease-associated phenotype identifies a test substance that is likely to prevent or diminish the specific biological response in a subject having said inflammatory disease-associated genotype.

41. (New). The method of claim 40, wherein said inflammatory disease-associated genotype further comprises IL-1RN (+2018) allele 2, an IL-1RN (VNTR) allele, IL-1A (+48485) allele 2, or IL-1A (-889) allele 2.

42. (New). A method for identifying a substance that is likely to prevent or diminish a specific biological response in a subject having an inflammatory disease-associated genotype, said method comprising the steps of:

- a) providing a cell from a test subject, having an inflammatory disease-associated genotype comprising:
  - i) an IL-1B (-511) allele;
  - ii) an IL-1RN (+2018) allele or an IL-1RN (VNTR) allele;
  - iii) an IL-1A (+4845) allele or an IL-1A (-889) allele; and
  - iv) an IL-1A (+3954) allele;
- b) observing in said cell, or a cell propagated therefrom, a biomarker;
- c) contacting said cell with a test substance;
- e) observing again in said cell said biomarker; and
- e) contacting said cells with an inducer prior to or concomitant observing said biomarker,

wherein a change in said biomarker from an inflammatory disease-associated phenotype to a non-inflammatory disease-associated phenotype identifies a test substance that is likely to prevent or diminish the specific biological response in a subject.